REMARKS

The Office action mailed 13 November 2008, has been received and its contents carefully noted. Claims 37-46 were rejected and claims 47-57 were withdrawn from consideration. *Applicants note that claim 57 is improperly numbered and should be claim 56. However, in order to prevent the Request for Pre-Appeal Brief Review from being improper due to the prohibition against submission with an amendment, the claim numbering has not been corrected.* Reconsideration is respectfully requested.

Withdrawn Claims

The Examiner withdrew claims 47-57 based on an election by original prosecution.

Applicants respectfully submit that it is improper to withdraw claims 47-57 based on an election by original prosecution. Specifically, as correctly noted by the Examiner, Applicants originally elected claims directed to "rottlerin or a derivative thereof".

In the Office action mailed 9 November 2007, the claims were rejected under 35 U.S.C. 112, second paragraph, as the Examiner deemed that the term "derivative" was unclear. In response, Applicants argued that the definition of "derivative" with respect to rottlerin was defined in the Specification on page 43, paragraph 171 and submitted that the claims were therefore clear and definite.

Then in the Office action mailed 25 June 2008, the claims were rejected under 35 U.S.C. 112, first paragraph, as lacking written description and enabling support. Specifically, the Examiner deemed that use of the term "derivative" in claims 37 and 46 fail to meet the provisions of 35 U.S.C. 112, first paragraph, as the claims lacked chemical structural information. In response, Applicants separated the rottlerin "derivative" out from claims 37 and 46 by canceling the term from the claims and adding new claims 47-57 in order to recite the structural formula provide on page 43 of the Specification in order to address the written description and enablement rejections.

Now, in the Office action mailed 13 November 2008, the Examiner withdrew claims 47-57 and stated that the original claims as elected in response to a Restriction Requirement were directed to rottlerin or a derivative thereof and since the newly added claims are directed to a structural formula instead of rottlerin or a derivative thereof, claims 47-57 are withdrawn from

consideration as having been elected by original prosecution.

Applicants respectfully submit that the structural formula as set forth in claim 47 does in fact encompass rottlerin and a derivative of rottlerin as defined in the Specification on page 43. Therefore, Applicants respectfully submit that claims 47-57 were improperly withdrawn and request rejoinder of claims 47-57.

Rejection under 35 U.S.C. 103(a)

The Examiner rejected claims 37-46 under 35 U.S.C. 103(a) as being unpatentable over Schwartz (US 5,821,072), Gschwendt and Mouria. Specifically, the Examiner deemed that (1) Schwartz teaches that administration of a specific protein kinase C inhibitor is capable of potentiating apoptosis in pancreatic cancer; (2) Gschwendt discloses that rottlerin is a protein kinase C inhibitor; and (3) Mouria discloses that genistein causes apoptosis in pancreatic cancer cells. Thus, the Examiner deemed that it would have been obvious to administer rottlerin to treat pancreatic cancer (based on the combination of Schwartz and Gschwendt) and to further administer a second polyphenolic compound, genisten (Mouria). The Examiner noted that Applicants' prior arguments fail to be persuasive against the instant rejection because the Examiner deemed that Schwartz contemplates the use of PKC inhibitors to treat pancreatic cancer and that Mackay and Applicants did not provide evidence of any particular PKC inhibitor with respect to its duality of PKC activation and inhibition and pancreatic cancer.

ALL PKC inhibitors are not effective against pancreatic cancer cells

Applicants respectfully submit that one of ordinary skill in the art would not have a reasonable expectation of success in using **any** PKC inhibitor to treat pancreatic cancer. Specifically, as set forth in Example 9A of the instant Specification, **all** PKC inhibitors do not induce apoptosis in pancreatic cancer cells. In particular, **two** PKC inhibitors, GF109203X (GF) and Ro-32-0432 (Ro), do not cause apoptosis (as evidenced by oligonucleosomal DNA fragmentation) in MIA PaCa-2 cells and PANC-1 cells. See Figures 29 and 30.

Thus, **all** PKC inhibitors are not effective against pancreatic cancer. Therefore, the simple fact that rottlerin is a PKC inhibitor does not mean that rottlerin would be effective against pancreatic cancer. In fact, as set forth in the instant Specification, the ability of rottlerin

to cause apoptosis is independent of any effects it may have on PKC. Consequently, one of ordinary skill in the art would not have been motivated to use rottlerin (or a compound as specified in claim 47) to treat pancreatic cancer with a reasonable expectation of success.

The deficiencies of Schwartz

The teachings of Schwartz are significantly deficient and limited. Specifically, Schwartz teaches that a specific PKC inhibitor (i.e. safingol or RO 32-0432) is capable of potentiating apoptosis in tumor cells **if** administered along with (i.e. during or prior to) the administration of an antitumor therapeutic agent, such as Mitomycin C (MMC). See col. 2, lines 56-61; and col. 3, lines 2-4. Schwartz teaches that treatment with a PKC inhibitor alone does not induce apoptosis in cancer cells. See col. 7, lines 35-37 ("safingol alone did not induce significant levels of apoptosis"); and col. 18, lines 48-49 (RO 32-0432 alone had "essentially no effect on inducing apoptosis"). Thus, Schwartz teaches that a PKC inhibitor such as safingol or RO 32-0432 can potentiate the apoptotic effect of a chemotherapeutic agent such as MMC. **In other words, Schwartz does not teach or suggest that a PKC inhibitor itself can induce apoptosis in a cancer.**

In addition, the experimental evidence of Schwartz is based only on gastric cancer cell lines. Although Schwartz recites a laundry list of cancers, including pancreatic cancer, that can be treated by the disclosed methods, no experimental evidence using a pancreatic cell line is provided.

Further, Schwartz makes no mention of rottlerin.

Thus, at most, Schwartz teaches that (1) a PKC inhibitor by itself does not induce apoptosis in a cancer cell, and (2) a PKC inhibitor must be administered with a chemotherapeutic agent in order to provide any increase in apopotosis in a gastric cancer cell as compared with a control.

Consequently, Schwartz does not teach or suggest that (1) any PKC inhibitor, (2) such as rottlerin, (3) by itself induces apoptosis in (4) pancreatic cancer.

Gschwendt and Mouria do not alleviate the deficiencies of Schwartz

Gschwendt does not alleviate the deficiencies of Schwartz. In particular, Gschwendt

merely discloses that rottlerin is a PKC inhibitor with specificity for certain PKC isozymes and that derivatives of rottlerin might have improved selectivity for a given PKC isozyme. Nowhere does Gschwendt teach or suggest that rottlerin by itself induces apoptosis in pancreatic cancer.

Similarly, Mouria mentions nothing about rottlerin. Mouria simply discloses that quercetin and genisten may be used to treat pancreatic cancer.

Consequently, Schwartz, Gschwendt and Mouria, alone or in combination, do not teach or suggest that rottlerin can be used to treat pancreatic cancer with a reasonable expectation of success.

Therefore, the claimed invention is unobvious and the rejection under 35 U.S.C. 103(a) should properly be withdrawn.

Declaration of Dr. Jingzhen Yuan

Applicants submit herewith the Declaration of Dr. Yuan in support of the arguments provided herein. As provided in the declaration, Dr. Yuan states that it is her opinion that the Examiner's reasoning for rejecting the claims is flawed as it is based on the implied (and incorrect) assertion that Schwartz teaches that all PKC inhibitors will be effective (e.g. induce apoptosis) against pancreatic cancer cells. In particular, Dr. Yuan states that experimental evidence in the art proves that all PKC inhibitors are not effective against in pancreatic cancer cells. Since all PKC inhibitors are not effective against cancer, and the specific PKC inhibitors tested by themselves, as taught by Schwartz, do not induce apoptosis in cancer cells, Dr. Yuan states that, in her opinion, one of ordinary skill in the art would not have been motivated to combine the teachings of Schwartz and Gschwendt in order to treat or inhibit pancreatic cancer or pancreatitis in a subject by administering rottlerin or a derivative thereof (i.e. a compound as set forth in claim 47) with a reasonable expectation of success. Dr. Yuan also states that the disclosures of Schwartz, Gschwendt and Mouria, alone or in combination, do not provide the requisite teaching, suggestion or motivation for one of ordinary skill in the art to administer rottlerin or a derivative thereof (i.e. a compound as set forth in claim 47) to treat or inhibit pancreatic cancer or pancreatitis in a subject with a reasonable expectation of success.

In view of the arguments provided herein which are supported by experimental evidence and the declaration of Dr. Yuan, Applicants respectfully submit that the claimed invention is

unobvious and therefore, the rejection under 35 U.S.C. 103(a) should properly be withdrawn.

Request for Interview

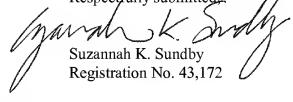
Either a telephonic or an in-person interview is respectfully requested should there be any remaining issues.

CONCLUSION

All of the stated grounds of objection and rejection have been properly traversed, accommodated, or rendered moot. Therefore, it is respectfully requested that the Examiner reconsider all presently outstanding objections and rejections and that they be withdrawn. It is believed that a full and complete response has been made to the outstanding Office action and, as such, the present application is in condition for allowance. If the Examiner believes, for any reason, that personal communication will expedite prosecution of this application, the Examiner is invited to telephone the undersigned at the number provided.

It is not believed that extensions of time are required, beyond those that may otherwise be provided for in accompanying documents. However, in the event that additional extensions of time are necessary to prevent abandonment of this application, then such extensions of time are hereby petitioned under 37 C.F.R. 1.136(a), and any fees required therefor are hereby authorized to be charged to **Deposit Account No. 02-4300**, Attorney Docket No. **034044.021CIP1**.

Respectfully submitted,



Suzannah K. Sundby
Registration No. 43,172

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SMITH, GAMBRELL & RUSSELL, LLP
1130 Connecticut Ave., NW, #1130
Washington, D.C. 20036
Telephone: (202) 263-4332
Fax: (202) 263-4352
ssundby@sgrlaw.com